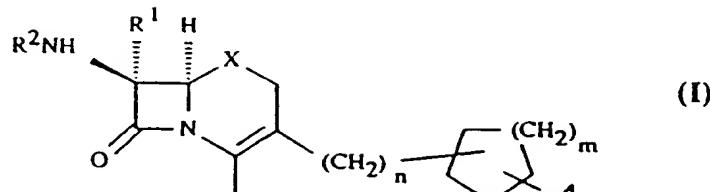


Claims

*Add B1*

1. A compound of formula (I) or a salt thereof:

5



10

wherein

$R^1$  is hydrogen, methoxy or formamido;

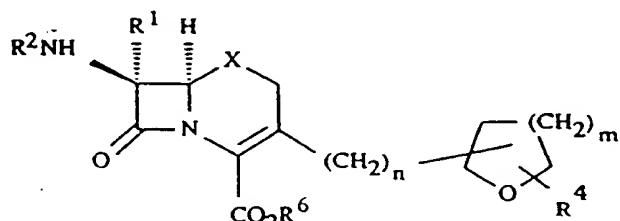
$R^2$  is an acyl group;

$CO_2R^3$  is a carboxy group or a carboxylate anion, or  $R^3$  is a 15 readily removable carboxy protecting group;

$R^4$  represents up to four substituents selected from alkyl, alkenyl, alkynyl, ~~alkoxy~~, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino,  $CO_2R$ ,  $CONR_2$ ,  $SO_2NR_2$  (where R is hydrogen or  $C_{1-6}$  alkyl), aryl and heterocyclyl, 20 which may be the same or different and wherein any  $R^4$  alkyl substituent is optionally substituted by any other  $R^4$  substituent; X is S, SO,  $SO_2$ , O or  $CH_2$ ; m is 1 or 2; and n is 0.

25 2. A compound as claimed in claim 1 having the formula (Ia):

30



(Ia)

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wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $m$ ,  $n$  and  $X$  are as defined with respect to formula (I) in claim 1 and the group  $CO_2R^6$  is  $CO_2R^3$  where  $CO_2R^3$  is a carboxy group or a carboxylate anion, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

3. A compound as claimed in claim 1 or claim 2 wherein  $R^1$  is hydrogen.

10 4. A compound as claimed in claim 1, 2 or 3 wherein  $R^2$  is an acyl group of formula (a) to (f):

15



20



25



30



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wherein p is 0, 1 or 2; m is 0, 1 or 2; A<sub>1</sub> is C<sub>1-6</sub> alkyl, substituted C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic or heteroaromatic group; X<sub>1</sub> is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclamino, guanidino or acylureido group; A<sub>2</sub> is an aromatic or heteroaromatic group, a substituted alkyl group; or a substituted dithietane; X<sub>2</sub> is a -CH<sub>2</sub>OCH<sub>2</sub>-, -CH<sub>2</sub>SCH<sub>2</sub>- or alkylene group; X<sub>3</sub> is an oxygen 10 or sulphur atom; A<sub>3</sub> is an aryl or heteroaryl group; and A<sub>4</sub> is hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy carbonyl(C<sub>1-6</sub>) alkyl, C<sub>2-6</sub> alkenyl, carboxy(C<sub>1-6</sub>)alkyl, C<sub>2-6</sub> alkynyl, aryl or C<sub>1-6</sub>alkyl substituted by up to three aryl groups.

15

5. A compound as claimed in claim 4 wherein A<sub>1</sub> is optionally substituted phenyl, X<sub>1</sub> is hydrogen or amino, A<sub>2</sub> is optionally substituted phenyl, X<sub>3</sub> is oxygen, A<sub>3</sub> is aminothiazolyl, aminothiadiazolyl or furyl, and R<sub>4</sub> is 20 hydrogen, C<sub>1-6</sub> alkyl, or carboxy C<sub>1-6</sub> alkyl.

6. A compound as claimed in any one of claims 1 to 5 wherein CO<sub>2</sub>R<sup>3</sup> is carboxy or a carboxylate anion or R<sup>3</sup> is t-butyl, 4-methoxybenzyl, diphenylmethyl, acetoxyethyl, 25 acetoxyethyl, pivaloyloxymethyl, propan-2-yloxycarbonyl-oxyethyl or 2-ethoxycarbonyl-but-2-enyl.

7. A compound as claimed in any one of claims 1 to 6 wherein the cyclic ether group bonded to the 3-position of 30 the cephalosporin nucleus is unsubstituted or unsubstituted by up to three substituents selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkanoyloxy C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy C<sub>1-6</sub> alkyl.

35 8. A compound as claimed in any one of claims 1 to 7 wherein m is 1.

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9. A compound as claimed in any one of claims 1 to 8 wherein the cyclic ether group is a tetrahydrofuran-2-yl or a tetrahydropyran-2-yl group.

5 10. Sodium  $(6R, 7R)$ -7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(RS)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

11. Pivaloyloxyethyl  $(6R, 7R)$ -7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(RS)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

12. Sodium  $(6R, 7R)$ -7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(RS)$ -tetrahydropyran-2-yl]-15 ceph-3-em-4-carboxylate.

13. Pivaloyloxyethyl  $(6R, 7R)$ -7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(RS)$ -tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

20 14.  $(6R, 7R)$ -7-[2-(2-Aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-[ $(RS)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylic acid.

25 15. Sodium  $(6R, 7R)$ -7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(S)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

16. Pivaloyloxyethyl  $(6R, 7R)$ -7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[ $(S)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

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17. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

5 18. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

19. Diphenylmethyl (6R, 7R)-7-phenylacetamido-3-[(RS)-10 tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

20. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

15

21. Acetoxyethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

20 22. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxymethyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate

23. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-(Z)-pent-2-enamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

24. Sodium (6R, 7R)-7-[2-(2-Aminothiadiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-30 em-4-carboxylate.

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25. (RS)-1-Acetoxyethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

5 26. (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-carboxy-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylic acid disodium salt.

27. Sodium (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)-acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

10 28. Sodium (1S,6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1-oxide.

15 29. Sodium 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxy-iminoacetamido]-3-(tetrahydrofuran-2-yl)-1-carba-1-dethia-ceph-3-em-4-carboxylate.

20 30. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxy-iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1,1-dioxide.

25 31. (RS)-1-(Propan-2-yl)oxycarbonyloxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

30 32. Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(5R,2S)-5-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

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33. Sodium (6R, 7R)-7-[2-(furan-2-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

5 34. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-5,5-dimethyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

10 35. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxycarbonyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

15 36. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[3-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

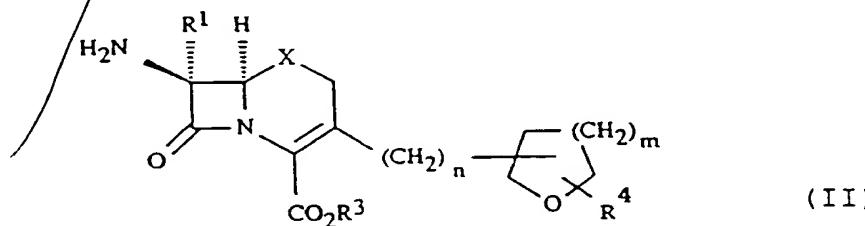
20 37. 2-Ethoxycarbonyl-(Z)-but-2-enyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

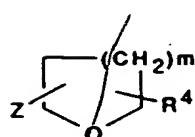
38. A compound of formula (I) as defined in claim 1 substantially as hereinbefore described with reference to the preparative examples.

25 39. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 28 which process comprises:

30 (a) treating a compound of formula (II) or a salt thereof:

35





(xI)

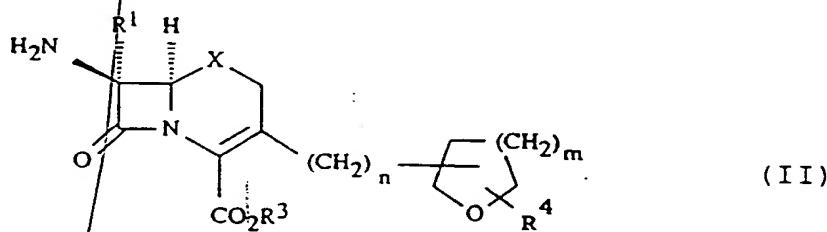
10 and thereafter, if necessary or desired, carrying out one of  
the following steps:

15

- i) removing any protecting groups;
- ii) converting the group  $\text{CO}_2\text{R}^3$  to a different group  $\text{CO}_2\text{R}'^3$ ;
- iii) converting the group  $\text{R}^2$  to a different group  $\text{R}'^2$ ;
- 20 iv) converting the group X to a different group X';
- v) converting the product into a salt.

40. A process for the preparation of a compound of formula  
25 (I) substantially as hereinbefore described in the  
preparative Examples.

41. A compound of formula (II) or a salt thereof:



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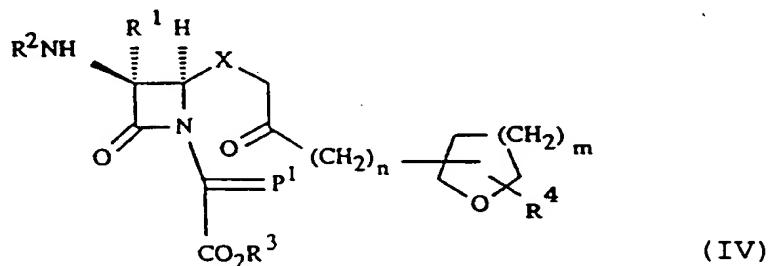
wherein  $R^1$ ,  $CO_2R^3$ ,  $R^4$ ,  $m$ ,  $n$ , and  $X$  are as hereinbefore defined with respect to formula (I) in claim 1, wherein any reactive group may be protected, and wherein the amino group is optionally substituted with a group which permits - 5 acylation to take place, with an N-acylating derivative of an acid of formula (III):



10

wherein  $R^2$  is as hereinbefore defined with respect to formula (I) in claim 1 and wherein any reactive group may be protected; or

15 (b) cyclising a compound of formula (IV):

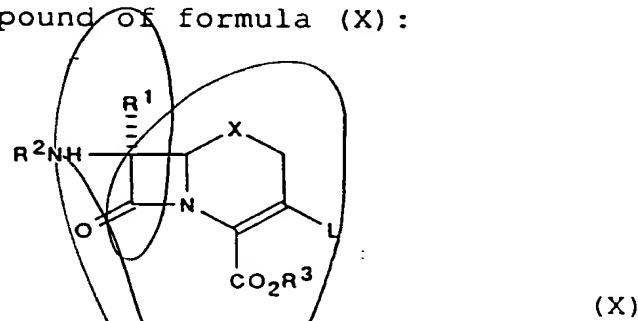


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wherein  $X$ ,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $m$ ,  $n$  and  $CO_2R^3$  are as hereinbefore defined with respect to formula (I) in claim 1 and  $P'$  is a 25 phosphorus residue; or

(c) treating a compound of formula (X):

30



35 wherein  $R^1$ ,  $R^2$ ,  $CO_2R^3$  and  $X$  are as hereinbefore defined with respect to formula (I) in claim 1, and  $L$  is a leaving group, with a compound of formula (XI):

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wherein  $R^1$   $CO_2R^3$ ,  $R^4$ ,  $X$ ,  $m$  and  $n$  are as hereinbefore defined with respect to formula (I) in claim 1.

42.  $t$ -Butyl  $6R,7R$ -7-Amino-3-(tetrahydrofuran-2-yl)-5-ceph-3-em-4-carboxylate.

43.  $t$ -Butyl  $(6R,7R)$ -7-Amino-3-[ $(RS)$ -tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

10 44. 4-Methoxybenzyl  $(6R,7R)$ -7-amino-3-(tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

45. Pivaloyloxymethyl  $(6R,7R)$ -7-amino-3-(tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

15 46.  $t$ -Butyl  $(6R,7R)$ -7-Amino-3-[ $(RS)$ -tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

47. Acetoxymethyl  $(6R,7R)$ -7-amino-3-[ $(S)$ -tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

48. 4-Methoxybenzyl  $(6R,7R)$ -7-Amino-3-(5-methoxymethyl-tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

25 49. 4-Methoxybenzyl  $(6RS,7SR)$ -7-amino-3-(tetrahydrofuran-2-yl)-1-carba-1-dethiaceph-3-em-4-carboxylate.

50. 4-Methoxybenzyl  $(6R,7R)$ -7-amino-3-(5-methyl-tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

30 51. A compound of formula (II) as defined in claim 41 substantially as hereinbefore described with reference to the preparative Examples.

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52. A pharmaceutical composition comprising a compound of formula (Ia) as defined in claim 2 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, and a pharmaceutically acceptable carrier.

5

53. A pharmaceutical composition as claimed in claim 52 further comprising a  $\beta$ -lactamase inhibitor.

54. A compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined in claim 2, for use as a therapeutic agent.

55. A method of treating bacterial infections in humans and animals which comprises administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, to a human or animal.

56. The use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, for the manufacture of a medicament for the treatment of bacterial infections.